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(71) Applicant (for all designated States except US): **RANBAXY LABORATORIES LIMITED** [IN/IN]; 19, Nehru Place, New Delhi, 110 019 New Delhi (IN).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **KUMAR, Yatendra** [IN/IN]; U-26/5, Phase - III, DLF Qutab Enclave, 122001 Guragon, Haryana (IN). **TEWARI, Neera** [IN/IN]; K-10/19 (First Floor), Phase - II, DLF Qutab Enclave, 122001 Guragon, Haryana (IN). **ARYAN, Ram, Chander** [IN/IN]; 1066, Sector A, Pocket A, Vasant Kunj, 110070 New Delhi, Delhi (IN). **RAI, Bishwa, Prakash** [IN/IN]; Jagdish Pur, Sohauily, 276306 Azamgarh, Uttar Pradesh (IN). **AHUJA, Seema** [IN/IN]; 328, Railway Park Road, Hapur, 245101 Ghaziabad, Uttar Pradesh (IN).

(74) Common Representative: **RANBAXY LABORATORIES LIMITED**; c/o Jayadeep R. Deshmukh, 600 College Road East, Suite 2100, Princeton, NJ 08540 (US).

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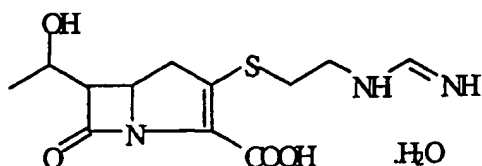
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(54) Title: PROCESS FOR THE PREPARATION OF CRYSTALLINE N-FORMIMIDOYL THIENAMYCIN MONOHYDRATE (IMIPENEM MONOHYDRATE)



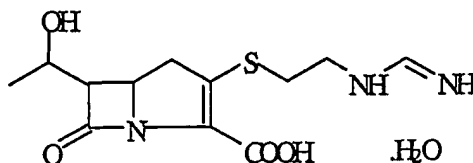
(I)

(57) Abstract: The present invention relates to a cost effective and commercially viable process for the preparation of crystalline N-formimidoyl thienamycin monohydrate (Imipenem monohydrate) of Formula I.

**PROCESS FOR THE PREPARATION OF CRYSTALLINE N-FORMIMIDOYL
THIENAMYCIN MONOHYDRATE (IMIPENEM MONOHYDRATE)**

FIELD OF THE INVENTION

5 The present invention relates to a cost effective and commercially viable process for the preparation of crystalline N-formimidoyl thienamycin monohydrate (Imipenem monohydrate) of Formula I:



FORMULA I

BACKGROUND OF THE INVENTION

15 Imipenem monohydrate, the crystalline monohydrate of N-formimidoyl derivative of thienamycin of Formula I, is the first clinically available member of a new class of β -lactam antibiotic that possess the carbapenem ring system. Imipenem exhibits an extremely broad spectrum of activity against gram-positive and gram-negative aerobic and anaerobic species, which is partly due to its high stability in presence of β -lactamases.

20 Imipenem was initially obtained by lyophilization technique as disclosed in US Patent No. 4,194,047. An alternate process of freeze crystallization or

lyophilization has been reported by M. Connolly et. al in J. Pharm. Sci, 85, 174-175 (1996). However, lyophilized product so obtained is often found to be largely amorphous which is thermodynamically unstable. A crystalline monohydrate form of imipenem is disclosed in US Patent No. 4,260,543, which is obtained by crystallization of a lyophilized sample of imipenem and was found to have unexpected stability in the solid state over the lyophilized form (amorphous form). However, it is reported that the changes in lyophilization conditions can change the degree of crystallinity of the final product. Crystallinity is of interest in the study of lyophilized imipenem because crystalline imipenem is more thermodynamically stable than amorphous or disordered imipenem. Processes of obtaining crystalline imipenem as described in the prior art requires specialized equipment such as freeze dryer or a lyophilizer which renders it unattractive at a commercial scale and also do not produce the product having consistent degree of crystallinity.

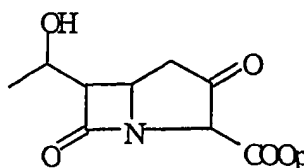
SUMMARY OF THE INVENTION

It is an object of the present invention to provide a cost effective and commercially viable process for producing highly pure thermally stable crystalline imipenem monohydrate having uniform degree of crystallinity directly from an aqueous solution obtained from the reaction mixture without involving lyophilization at any stage.

More particularly, the present invention relates to a process for the preparation of crystalline N-formimidoyl thienamycin monohydrate (imipenem monohydrate) of Formula I which comprises

(a) activating a keto ester compound of Formula II

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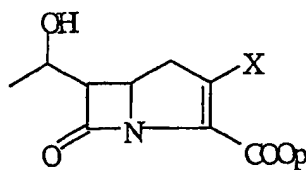


FORMULA II

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wherein p is hydrogen or a protecting group, in the presence of a suitable secondary amine, in a suitable N-substituted lactam or N, N-disubstituted amide as a solvent, optionally in combination with an inert organic solvent to obtain an activated keto ester of Formula III

15



FORMULA III

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wherein X is $OP(O)(OR)_2$ or $OS(O)_2R$ and R is C_{1-6} alkyl, C_{1-6} alkaryl, aryl or perfluoro C_{1-6} alkyl. The term alkyl refers to a straight or branched chain and when of sufficient size, may be cyclic. Preferred straight or branched alkyl groups include methyl, ethyl, propyl,

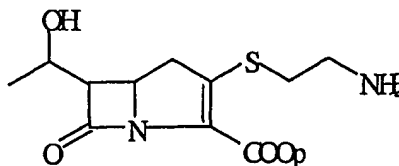
isopropyl, butyl and t-butyl. Preferred cycloalkyl groups include cyclopropyl, cyclopentyl, cyclohexyl and cyclopropyl methyl. The term aryl refers to aromatic rings including phenyl, substituted phenyl and naphthyl. Aryl groups may be substituted with one to three
5 substituents independently selected from a halogen, alkyl and halogenated lower alkyl group, wherein alkyl has the same meaning as defined above.

The protecting group p may be any of the readily removable carboxyl protecting groups. Preferably, p can be selected from the
10 group consisting of benzyl, p-nitrobenzyl and methoxymethyl.

The suitable secondary amine is selected from the group consisting of diisopropylamine, dicyclohexylamine, 2,2,6,6-tetramethylethyl piperidine (TMP) and 1,1,3,3-tetramethylguanide (TMG).

15 The suitable N-substituted lactam is selected from the group consisting of N-methyl-pyrrolidone (NMP), N-ethyl-pyrrolidone (NEP), N-methyl piperidinone and 1,3-dimethyl 3,4,5,6-tetrahydro-2(H) pyrimidinone (DMPH). The suitable N, N-disubstituted amide is
20 selected from the group consisting of dimethylformamide (DMF), dimethylacetamide (DMAc) and optional inert organic solvent is preferably tetrahydrofuran. The reaction is carried out at a temperature ranging between -20 to -70°C. The compound of Formula II may be prepared using methods known in the art.

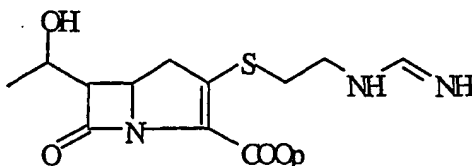
(b) Reacting the activated keto ester of Formula III, in situ with 2-aminoethanethiol (cysteamine) or with its salt in the presence of a secondary amine in N-substituted lactam or N, N-disubstituted amide at a temperature ranging from -80°C to -40°C to get thienamycin ester of Formula IV



FORMULA IV

wherein p, N-substituted lactam and N, N-disubstituted amine have the same meanings as defined above.

(c) Reacting thienamycin ester of Formula IV, in situ with benzyl formimidate hydrochloride ($\text{C}_6\text{H}_5\text{CH}_2\text{OCH}=\text{NH}_2^+\text{Cl}^-$) in the presence of a secondary amine in N-substituted lactam or N, N-disubstituted amide to get amidine carboxylate ester (blocked N - formimidoyl thienamycin) of Formula V



FORMULA V

wherein p, N-substituted lactam and N, N-disubstituted amide have the same meanings as defined above.

(d) Hydrogenation of the blocked N-formimidoyl thienamycin of Formula V to get imipenem and the solution containing the reaction mixture is subjected to dianion chromatography, followed by crystallization in the presence of a suitable alcohol or a ketone as a co-solvent to yield highly pure crystalline N-formimidoyl thienamycin monohydrate (imipenem monohydrate). Suitable alcohol and ketone may be selected from ethanol, isopropanol, acetone and methyl isobutyl ketone.

DETAILED DESCRIPTION OF THE INVENTION

In the following section one preferred embodiment is described by way of example to illustrate the process of this invention. However, these are not intended in any way to limit the scope of the present invention.

EXAMPLE 1

PREPARATION OF CRYSTALLINE IMIPENEM MONOHYDRATE

Step 1 - Preparation of (5R, 6S) p-Nitrobenzyl-3-(diphenylphosphono)-6-[(1R)-1-hydroxyethyl]-1-azabicyclo[3.2.0] hept-2-ene-7-one-2-carboxylate

To a solution of p-nitrobenzyl (5R, 6S)p-Nitrobenzyl-6-[(1R)-1-hydroxyethyl]-1-azabicyclo[3.2.0]heptan-3,7-dione-2-carboxylate (20.0g, 57mmol) in a mixture of tetrahydrofuran and 1,3-dimethyl-3,4,5,6-tetrahydro (2H) pyrimidinone (160 ml; 1:1 v/v) was added diisopropylamine (7.0g, 69mmol) at -25 to -30°C followed by diphenylchlorophosphate (17.0g, 63mmol). The mixture was stirred for 40-45 min. at -10 to -15°C and used in the next step without isolation of the enol phosphate intermediate.

Step II - Preparation of (5R,6S) p-Nitrobenzyl-3-[(2-aminoethyl)thio]-6-[(1R)-1-hydroxyethyl]-1-azabicyclo [3.2.0] hept-2-ene-7-one-2-carboxylate

The reaction mixture from Step I was cooled to -75°C. A solution of cysteamine (2-aminoethanethiol) hydrochloride (7.2g, 63mmol) in 1,3-dimethyl-3,4,5,6-tetrahydro (2H) pyrimidinone (70ml) and diisopropylamine (7.0g, 69 mmol) was added at -75 to -50°C in 10 min. The reaction mixture thus obtained was further stirred at -40°C to -45°C for about 1 hr and was used as such without its isolation.

Step III - Preparation of (5R,6S) p-Nitrobenzyl-3-[2-[(iminomethyl)amino]ethyl]thio]-6-[(1R)-1-hydroxyethyl]-1-azabicyclo[3.2.0]hept-2-ene-7-one-2-carboxylate

The reaction mixture from Step II was cooled to -45°C, and diisopropylamine (8.7g, 86mmol) was added followed by benzylformimidate hydrochloride (12.8g, 74.6mmol). The resulting mixture was stirred at -45 to -

40°C for about 30 minutes and then at -20 to -15°C for about 1 hour 30 minutes. Tetrahydrofuran (200ml) was added at -20 to -15°C and diisopropylamine salts were filtered off from the reaction mixture. The filtrate contained the N-formamidoyl thienamycin PNB ester.

- 5 Step IV - Preparation of [5R- [5 α , 6 α (R*)]]-6-(1-hydroxyethyl)-3-[[2-
[(iminomethyl)amino]ethyl]thio]-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-
carboxylic acid

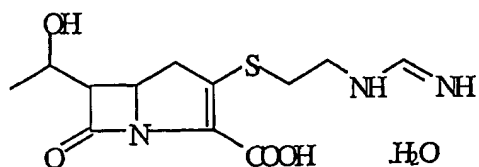
The filtrate from Step III containing PNB-N-formimidoyl thienamycin was poured into a mixture of water (400ml), N-methylmorpholine (18g),
10 isopropyl alcohol (200ml) at 0-5°C and at pH of about 7.0. The reaction mixture was then hydrogenated over at 3-4 kg of hydrogen pressure at 5-10°C. The reaction mixture was filtered, extracted with methylene chloride (2 x 300ml) and the aqueous layer was separated. The aqueous layer was concentrated to 200ml by distillation under reduced pressure. The
15 concentrated solution was purified by dianion chromatography using water as an eluent. The fractions containing the desired product were combined and concentrated either under reduced pressure or using plain membrane type reverse osmosis techniques to a volume of 50ml. The concentrated solution was then cooled to 0-5°C and isopropyl alcohol (25ml) was added to it. It was
20 further stirred for 40-45 min at the same temperature. Another lot of isopropyl alcohol (25ml) was added and stirring continued for about 1 hour at 0-5°C. The crystalline precipitate obtained was filtered, washed with isopropyl alcohol and acetone (2 x 10ml) and dried to yield 4.0g of crystalline N-formimidoyl thienamycin.

X-ray diffraction pattern (Figure 1) shows peaks characteristic of crystalline form of imipenem monohydrate as obtained per US Patent No. 4,260,543; Purity by HPLC = 99.23%.

5 While the present invention has been described in terms of its specific embodiments, certain modifications and equivalents will be apparent to those skilled in the art and are intended to be included within the scope of the present invention.

WE CLAIM:

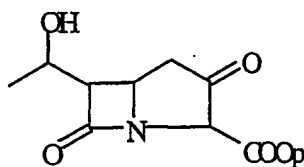
1. A process for the preparation of crystalline N-formimidoyl thienamycin monohydrate (imipenem) of Formula I



FORMULA I

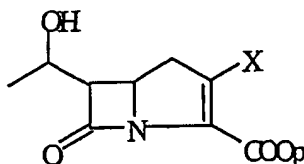
which comprises

- (a) activating a keto ester compound of Formula II



FORMULA II

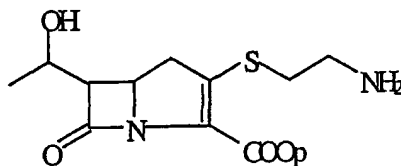
wherein p is hydrogen or a protecting group, in the presence of a suitable secondary amine, in a suitable N-substituted lactam or N, N-disubstituted amide as a solvent, optionally in combination with an inert organic solvent to obtain a compound of Formula III



FORMULA III

wherein x is OP(O)(OR)_2 or $\text{OS(O)}_2\text{R}$ and R is C_{1-6} alkyl, C_{1-6} alkaryl, aryl or perfluoro C_{1-6} alkyl; the term alkyl refers to a straight or branched chain and when of sufficient size, may be cyclic, preferred straight or branched alkyl groups include methyl, ethyl, propyl, isopropyl, butyl and t-butyl, preferred cycloalkyl groups include cyclopropyl, cyclopentyl, cyclohexyl and cyclopropyl methyl; the term aryl refers to aromatic rings including phenyl, substituted phenyl and naphthyl, aryl groups may be substituted with one to three substituents independently selected from halogen, alkyl and halogenated lower alkyl group, wherein alkyl has the same meaning as defined above,

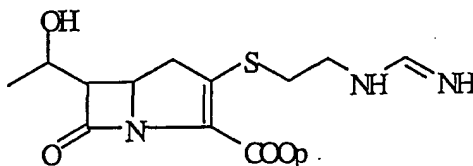
(b) reacting the activated keto ester of Formula III in situ with 2-aminoethanethiol (cysteamine) or its salt in the presence of a secondary amine in a N-substituted lactam or N, N-disubstituted amide as a solvent to get thienamycin ester of Formula IV



FORMULA IV

wherein p, n-substituted lactam and N,N-disubstituted amine, have the same meaning as defined above,

(c) reacting thienamycin ester of Formula IV, in situ with benzyl formimidate hydrochloride ($C_6H_5CH_2OCH=NH_2^+Cl^-$) in the presence of a secondary amine in a N-substituted lactam or N, N-disubstituted amide to get amidine carboxylate ester (blocked N-formimidoyl thienamycin) of Formula V



FORMULA V

wherein p, N-substituted lactam and N,N-disubstituted amine, have the same meaning as defined above,

(d) hydrogenating the blocked N-formimidoyl thienamycin of Formula V, to yield N-formimidoyl thienamycin (imipenem) in a solution and subjecting the solution containing the reaction mixture to dianion chromatography followed by crystallization in the presence of an alcohol or a ketone co-solvent to yield highly pure crystalline N-formimidoyl monohydrate (imipenem monohydrate) of Formula I.

2. The process of claim 1 wherein protecting group p is selected from the group consisting of benzyl, p-nitrobenzyl and methoxymethyl.

3. The process of claim 1 wherein the suitable secondary amine is selected from the group consisting of diisopropylamine, dicyclohexyl amine, 2,2,6,6-tetramethylethyl piperidine (TMP) and 1,1,3,3-tetramethylguanide (TMG).

4. The process of claim 1 wherein N-substituted lactam or N, N-disubstituted amide is used alone or in combination with an inert solvent.

5. The process in accordance with claim 4 wherein N-substituted lactam is selected from the group consisting of N-methyl pyrrolidone (NMP), N-ethylpyrrolidone (NEP), N-methylpiperidone and 1,3-dimethyl-3,4,5,6-tetrahydro(2H) pyrimidinone.

6. The process in accordance with claim 4 wherein suitable N, N-disubstituted amide is selected from the group consisting of dimethylformamide (DMF) and dimethylacetamide (DMAc).

7. The process of claim 4 wherein inert solvent is tetrahydrofuran.

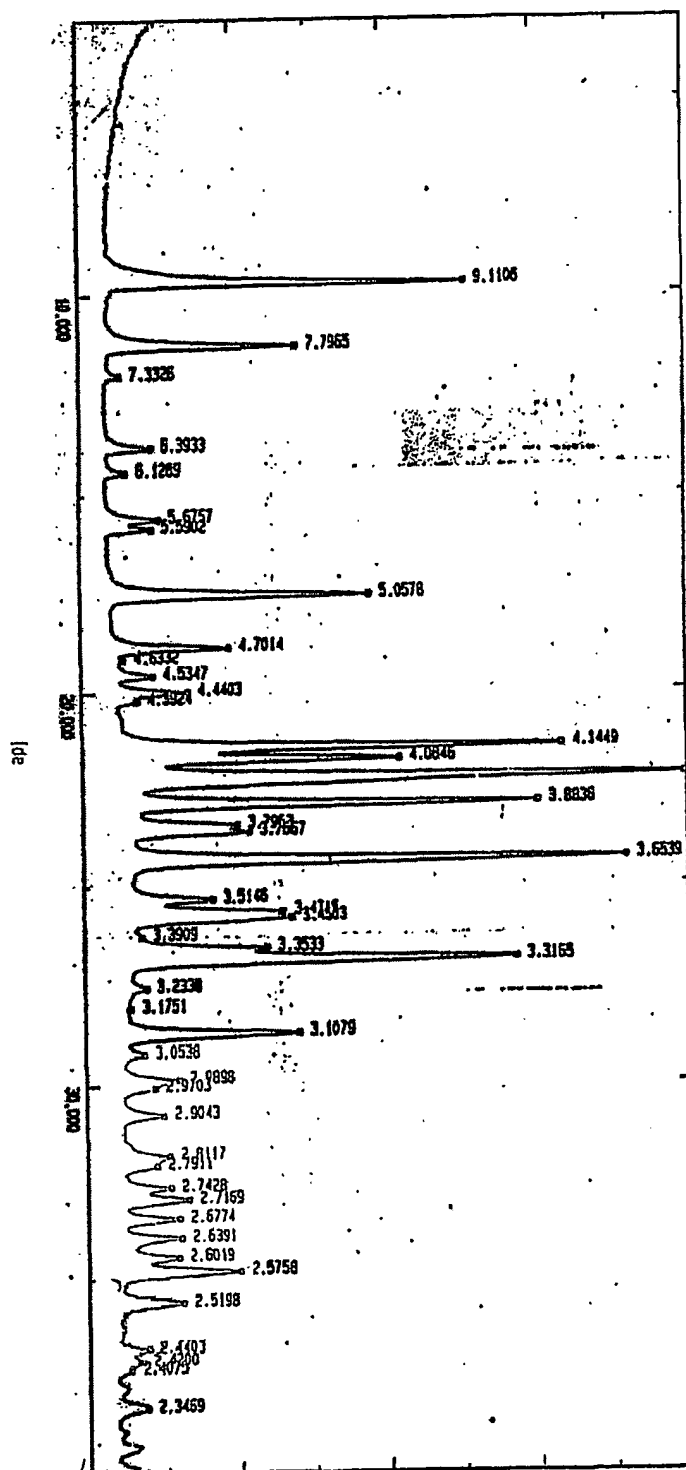
8. The process of claim 4 wherein a mixture of 1,3-dimethyl-3,4,5,6-tetrahydro-2(H) pyrimidinone and tetrahydrofuran is used as a solvent.

9. The process according to claim 1 wherein alcohol is selected from the group consisting of ethanol and isopropyl alcohol.

10. The process according to claim 1 wherein ketone is selected from the group consisting of acetone and methyl isobutyl ketone.

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Kumar et al.

Intensity (cps)



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INTERNATIONAL SEARCH REPORT

International Application No
PCT/IB 01/02069

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D477/20

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 245 069 A (MCMANUS JAMES W) 14 September 1993 (1993-09-14) column 9 -column 10	1-10
A	US 5 872 250 A (JOBSON RONALD B ET AL) 16 February 1999 (1999-02-16) the whole document	1-10
A	US 4 260 543 A (MILLER THOMAS W) 7 April 1981 (1981-04-07) cited in the application the whole document	1-10
A	US 4 194 047 A (CHRISTENSEN BURTON G ET AL) 18 March 1980 (1980-03-18) cited in the application claims	1-10

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

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Date of the actual completion of the international search

8 February 2002

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19/02/2002

Name and mailing address of the ISA

European Patent Office, P.B. 6818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Chouly, J

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/IB 01/02069

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5245069	A	14-09-1993	NONE
US 5872250	A	16-02-1999	NONE
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